ejpmr, 2020,7(5), 300-312

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

THREE MUSKETEERS OF PAIN PRECURSORS AND THEIR REMEDY

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Article Received on 07/03/2020 **Article Revised on 28/03/2020** **Article Accepted on 17/04/2020**

ABSTRACT

Pain is unwanted symptom of body malfunction which is not desired by anyone. It is of two types: superficial & neurogenic. Pain is generated by three biogenic precursors: prostaglandins, thromboxanes and leukotrienes. All three are C-20 carbon units having free carboxylic acid units which stimulate cyclooxygenase enzymatic pathway to produce sensation of pain. Feeling of pain is at nerve endings as superficial and generation from spinal cord to produce neurogenic pain. Pain produce inflammation which accumululate body fluids at a particular segment produce swelling and redness due to discharge of histamines to feel the sensation of pain. Pain can be controlled by two types of analgesic drugs: opioids and non-opioids. Generally morphine derivatives come in opioid analgesic and salicylates come under NSAIDs as non-opioids. Analgesic agents block arachidonic acid pathway by blocking phospholipase A_2 to block the further process in prostaglandin synthase, lipoxygenase and thromboxane synthase pathways to block the biosynthesis of COX1 & COX2 isozymes, LTAs & TXA and TXB.

KEYWORDS: Pain, Allodynia Pain, Phantom Pain, Asymbolia Pain, Idiopathic Pain, Nociceptive Pain, Neuropathic Pain, Visceral Pain, Nociplastic Pain, Pain Precursors, Eicosanoids, Arachidonic acid, Prostaglandin, Thromboxane, Leukotriene.

INTRODUCTION

Pain is a distressing feeling often caused by intense or damaging stimuli. The widely used definition defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". In medical diagnosis, pain is regarded as a symptom of an underlying condition. Pain motivates the individual to withdraw from damaging situations, to protect a damaged body part while it heals, and to avoid similar experiences in the future. Most pain resolves once the noxious stimulus is removed and the body has healed, but it may persist despite removal of the stimulus and apparent healing of the body. Sometimes pain arises in the absence of any detectable stimulus, damage or disease. Pain is the most common reason for physician consultation in most developed countries. It is a major symptom in many medical conditions, and can interfere with a person's quality of life and general functioning. Simple pain medications are useful in 20% to 70% of cases. Psychological factors such as social support, hypnotic suggestion, excitement, or distraction can significantly affect pain's intensity or unpleasantness. In some debates regarding physician-assisted suicide or euthanasia, pain has been used as an argument to permit people who are terminally ill to end their lives.[1]

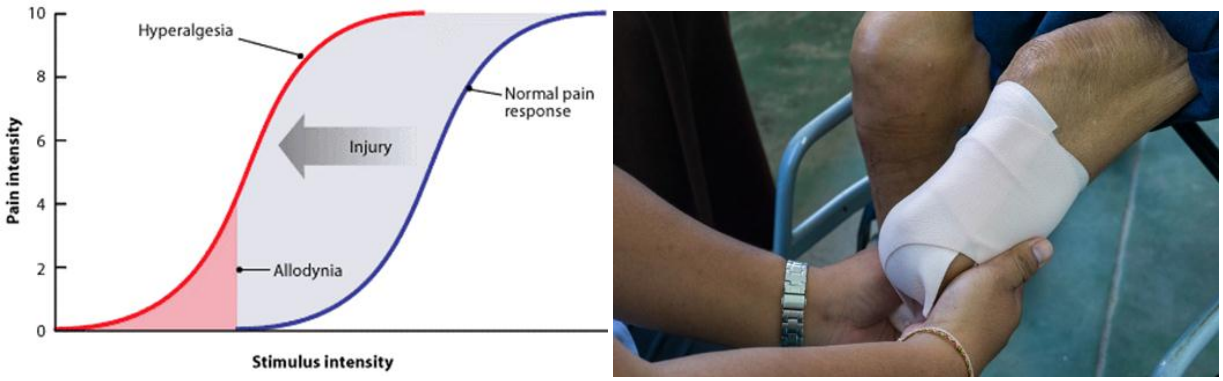


Figure 1: Allodynia and Phantom pain.

Classification

Duration

Pain is usually transitory, lasting only until the noxious stimulus is removed or the underlying damage or pathology has healed, but some painful conditions, such as rheumatoid arthritis, peripheral neuropathy, cancer and idiopathic pain, may persist for years. Pain that lasts a long time is called *chronic* or persistent, and pain that resolves quickly is called *acute*. Traditionally, the distinction between *acute* and *chronic* pain has relied upon an arbitrary interval of time between onset and resolution; the two most commonly used markers being 3 months and 6 months since the onset of pain, though some theorists and researchers have placed the transition from acute to chronic pain at 12 months. Others apply *acute* to pain that lasts less than 30 days, *chronic* to pain of more than six months' duration, and *subacute* to pain that lasts from one to six months. A popular alternative definition of *chronic pain*, involving no arbitrarily fixed durations, is "pain that extends beyond the expected period of healing". Chronic pain may be classified as cancer pain or else as benign.

Allodynia: Allodynia is pain experienced in response to a normally painless stimulus. It has no biological function and is classified by stimuli into dynamic mechanical, punctate and static. In osteoarthritis, NGF has been identified as being involved in allodynia. The extent and intensity of sensation can be assessed through locating trigger points and the region of sensation, as well as utilising phantom maps.[2,3]

Phantom: Phantom pain is pain felt in a part of the body that has been amputated, or from which the brain no longer receives signals. It is a type of neuropathic pain. The prevalence of phantom pain in upper limb amputees is nearly 82%, and in lower limb amputees is 54%. One study found that eight days after amputation, 72% of patients had phantom limb pain, and six months later, 67% reported it. Some amputees experience continuous pain that varies in intensity or quality; others experience several bouts of pain per day, or it may reoccur less often. It is often described as shooting, crushing, burning or cramping. If the pain is continuous for a long period, parts of the intact body may become sensitized, so that touching them evokes pain in the phantom limb. Phantom limb pain may accompany urination or defecation. Local anesthetic injections into the nerves or sensitive areas of the stump may relieve pain for days, weeks, or sometimes permanently, despite the drug wearing off in a matter of hours; and small injections of hypertonic saline into the soft tissue between vertebrae produces local pain that radiates into the phantom limb for ten minutes or so and may be followed by hours, weeks or even longer of partial or total relief from phantom pain. Vigorous vibration or electrical stimulation of the stump, or current from electrodes surgically implanted onto the spinal cord, all produce relief in some patients.[4]

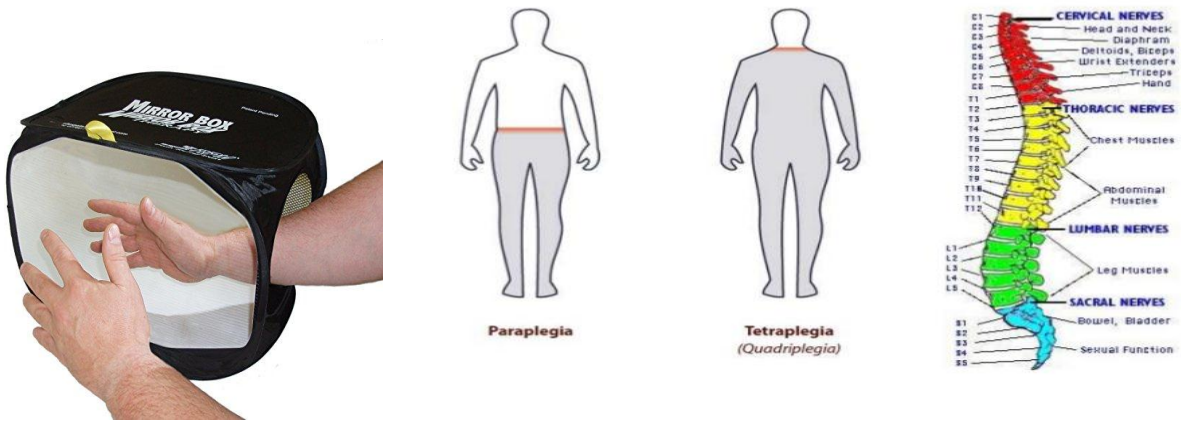


Figure 2: Mirrox box and spinal location of pain.

Mirror box therapy produces the illusion of movement and touch in a phantom limb which in turn may cause a reduction in pain. Paraplegia, the loss of sensation and voluntary motor control after serious spinal cord damage, may be accompanied by girdle pain at the level of the spinal cord damage, visceral pain evoked by a filling bladder or bowel, or, in five to ten per cent of paraplegics, phantom body pain in areas of complete sensory loss. This phantom body pain is initially described as burning or tingling, but may evolve into severe crushing or pinching pain, or the sensation of fire running down the legs or of a knife twisting in the flesh. Onset may be immediate or may not occur until years after the disabling injury. Surgical treatment rarely provides lasting relief.

Breakthrough

Breakthrough pain is transitory pain that comes on suddenly and is not alleviated by the patient's regular pain management. It is common in cancer patients who often have background pain that is generally well-controlled by medications, but who also sometimes experience bouts of severe pain that from time to time "breaks through" the medication. The characteristics of breakthrough cancer pain vary from person to person and according to the cause. Management of breakthrough

pain can entail intensive use of opioids, including fentanyl.

Asymbolia and insensitivity: The ability to experience pain is essential for protection from injury, and recognition of the presence of injury. Episodic analgesia may occur under special circumstances, such as in the excitement of sport or war: a soldier on the battlefield may feel no pain for many hours from a traumatic amputation or other severe injury. Although unpleasantness is an essential part of the IASP definition of pain, it is possible to induce a state described as intense pain devoid of unpleasantness in some patients, with morphine injection or psychosurgery. Such patients report that they have pain but are not bothered by it; they recognize the sensation of pain but suffer little, or not at all. Indifference to pain can also rarely be present from birth; these people have normal nerves on medical investigations, and find pain unpleasant, but do not avoid repetition of the pain stimulus.[5]

Three dimensions of pain

In 1968 Ronald Melzack and Kenneth Casey described chronic pain in terms of its three dimensions:

- "sensory-discriminative" (sense of the intensity, location, quality and duration of the pain),
- "affective-motivational" (unpleasantness and urge to escape the unpleasantness), and
- "cognitive-evaluative" (cognitions such as appraisal, cultural values, distraction and hypnotic suggestion).

They theorized that pain intensity (the sensory discriminative dimension) and unpleasantness (the affective-motivational dimension) are not simply determined by the magnitude of the painful stimulus, but "higher" cognitive activities can influence perceived intensity and unpleasantness. Cognitive activities "may affect both sensory and affective experience or they may modify primarily the affective-motivational dimension. Thus, excitement in games or war appears to block both dimensions of pain, while suggestion and placebos may modulate the affective-motivational dimension and leave the sensory-discriminative dimension relatively undisturbed." The paper ends with a call to action: "Pain can be treated not only by trying to cut down the sensory input by anesthetic block, surgical intervention and the like, but also by influencing the motivational-affective and cognitive factors as well."

Evolutionary and behavioral role

Pain is part of the body's defense system, producing a reflexive retraction from the painful stimulus, and tendencies to protect the affected body part while it heals, and avoid that harmful situation in the future. It is an important part of animal life, vital to healthy survival. People with congenital insensitivity to pain have reduced life expectancy.

Idiopathic: Idiopathic pain (pain that persists after the trauma or pathology has healed, or that arises without any apparent cause) may be an exception to the idea that pain is helpful to survival, although some psychodynamic psychologists argue that such pain is psychogenic, enlisted as a protective distraction to keep dangerous emotions unconscious.

Mechanism

Nociceptive: Nociceptive pain is caused by stimulation of sensory nerve fibers that respond to stimuli approaching or exceeding harmful intensity (nociceptors), and may be classified according to the mode of noxious stimulation. The most common categories are "thermal" (e.g. heat or cold), "mechanical" (e.g. crushing, tearing, shearing, etc.) and "chemical" (e.g. iodine in a cut or chemicals released during inflammation). Some nociceptors respond to more than one of these modalities and are consequently designated polymodal. Nociceptive pain may also be classed according to the site of origin and divided into "visceral", "deep somatic" and "superficial somatic" pain. Visceral structures (e.g., the heart, liver and intestines) are highly sensitive to stretch, ischemia and inflammation, but relatively insensitive to other stimuli that normally evoke pain in other structures, such as burning and cutting.

Visceral: Visceral pain is diffuse, difficult to locate and often referred to a distant, usually superficial, structure. It may be accompanied by nausea and vomiting and may be described as sickening, deep, squeezing, and dull. *Deep somatic* pain is initiated by stimulation of nociceptors in ligaments, tendons, bones, blood vessels, fasciae and muscles, and is dull, aching, poorly-localized pain. Examples include sprains and broken bones. *Superficial* pain is initiated by activation of nociceptors in the skin or other superficial tissue, and is sharp, well-defined and clearly located. Examples of injuries that produce superficial somatic pain include minor wounds and minor (first degree) burns.[6]

Neuropathic: Neuropathic pain is caused by damage or disease affecting any part of the nervous system involved in bodily feelings (the somatosensory system). Neuropathic pain may be divided into peripheral, central, or mixed (peripheral and central) neuropathic pain. Peripheral neuropathic pain is often described as "burning", "tingling", "electrical", "stabbing", or "pins and needles". Bumping the "funny bone" elicits acute peripheral neuropathic pain.[7]

Nociplastic: Nociplastic pain is pain characterized by a changed nociception (but without evidence of real or threatened tissue damage, or without disease or damage in the somatosensory system). This applies, for example, to fibromyalgia patients.

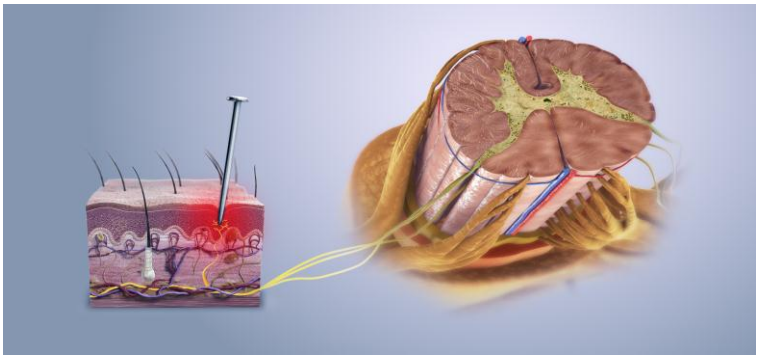


Figure-3: Nociception.

Psychogenic: Psychogenic pain, also called *psychalgia* or *somatoform pain*, is pain caused, increased, or prolonged by mental, emotional, or behavioral factors. Headache, back pain, and stomach pain are sometimes diagnosed as psychogenic. Sufferers are often stigmatized, because both medical professionals and the general public tend to think that pain from a psychological source is not "real". However, specialists consider that it is no less actual or hurtful than pain from any other source.

People with long-term pain frequently display psychological disturbance, with elevated scores on the Minnesota Multiphasic Personality Inventory scales of hysteria, depression and hypochondriasis (the "neurotic triad"). Some investigators have argued that it is this neuroticism that causes acute pain to turn chronic, but clinical evidence points the other direction, to chronic pain causing neuroticism. When long-term pain is relieved by therapeutic intervention, scores on the neurotic triad and anxiety fall, often to normal levels. Self-esteem, often low in chronic pain patients, also shows improvement once pain has resolved.[8]

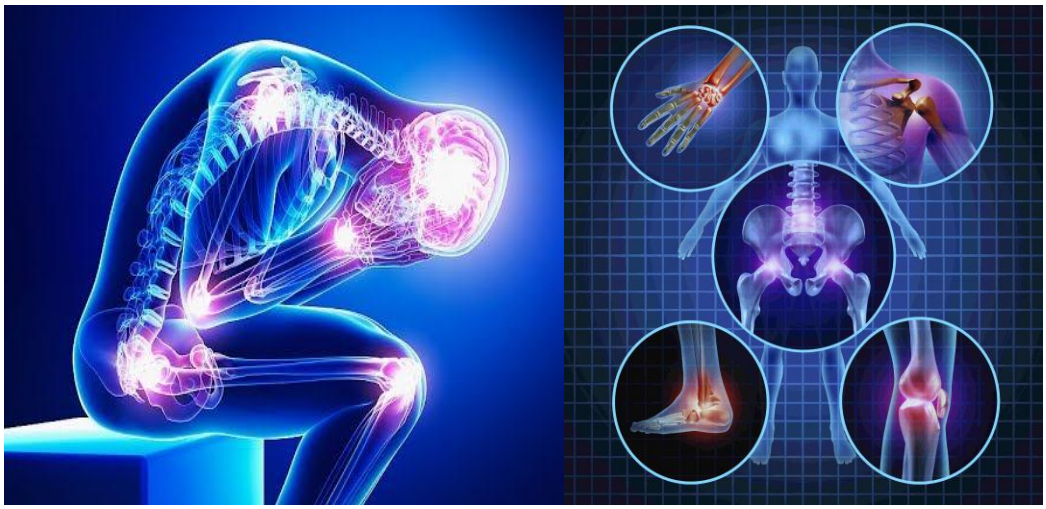


Figure 4: Pain.

Pain precursor: Prostaglandin

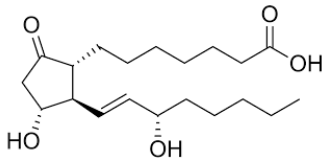
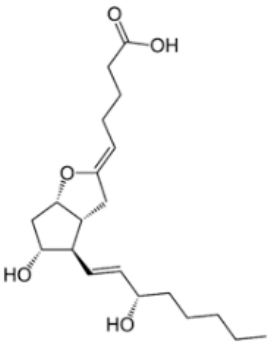


Figure-5: E_1 – Alprostadil.



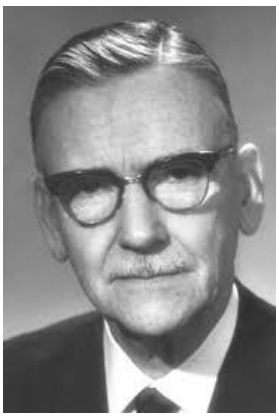
I_2 – Prostacyclin.

The **prostaglandins** (**PG**) are a group of physiologically active lipid compounds. These are called eicosanoids having diverse hormone-like effects in animals. Prostaglandins have been found in almost every tissue in humans and other animals. They are derived enzymatically from the fatty acid arachidonic acid. Every prostaglandin contains 20 carbon atoms, including a 5-carbon ring. They are a subclass of eicosanoids and of the prostanoid class of fatty acid derivatives.

The structural differences between prostaglandins account for their different biological activities. A given prostaglandin may have different and even opposite effects in different tissues in some cases. The ability of the same prostaglandin to stimulate a reaction in one tissue and inhibit the same reaction in another tissue is determined by the type of receptor to which the prostaglandin binds. They act as autocrine or paracrine factors with their target cells present in the immediate vicinity of the site of their secretion. Prostaglandins differ from endocrine hormones in that they are not produced at a specific site but in many places throughout the human body. Prostaglandins are powerful locally acting vasodilators and inhibit the aggregation of blood platelets. Through their role in vasodilation, prostaglandins are also involved in inflammation. They are biosynthesized in the walls of blood vessels and serve the physiological function of preventing needless clot formation, as well as regulating the contraction of smooth muscle tissue. Conversely, thromboxanes (produced by platelet cells) are vasoconstrictors and facilitate platelet aggregation. Their name comes from their role in clot formation (thrombosis). Specific prostaglandins are named with a letter (which indicates the type of ring structure) followed by a number (which indicates the number of double bonds in the hydrocarbon structure). For example, prostaglandin E_1 is abbreviated PGE_1 and prostaglandin I_2 is abbreviated PGI_2.

History and name

The name prostaglandin derives from the prostate gland, chosen when prostaglandin was first isolated from seminal fluid in 1935 by the Swedish physiologist Ulf von Euler, and independently by the Irish-English physiologist Maurice Walter Goldblatt (1895–1967). Prostaglandins were believed to be part of the prostatic secretions, and eventually were discovered to be produced by the seminal vesicles. Later, it was shown that many other tissues secrete prostaglandins and that they perform a variety of functions. The first total syntheses of prostaglandin $F_{2\alpha}$ and prostaglandin E_2 were reported by E. J. Corey in 1969, an achievement for which he was awarded the Japan Prize in 1989. In 1971, it was determined that aspirin-like drugs could inhibit the synthesis of prostaglandins. The biochemists Sune K. Bergström, Bengt I. Samuelsson and John R. Vane jointly received the 1982 Nobel Prize in Physiology or Medicine for their research on prostaglandins.[9]



Maurice Walter Goldblatt

E. J. Corey

Figure-6: Nobel Laureates: Sune K. Bergström, Bengt I. Samuelsson and John R. Vane.

Biosynthesis of eicosanoids

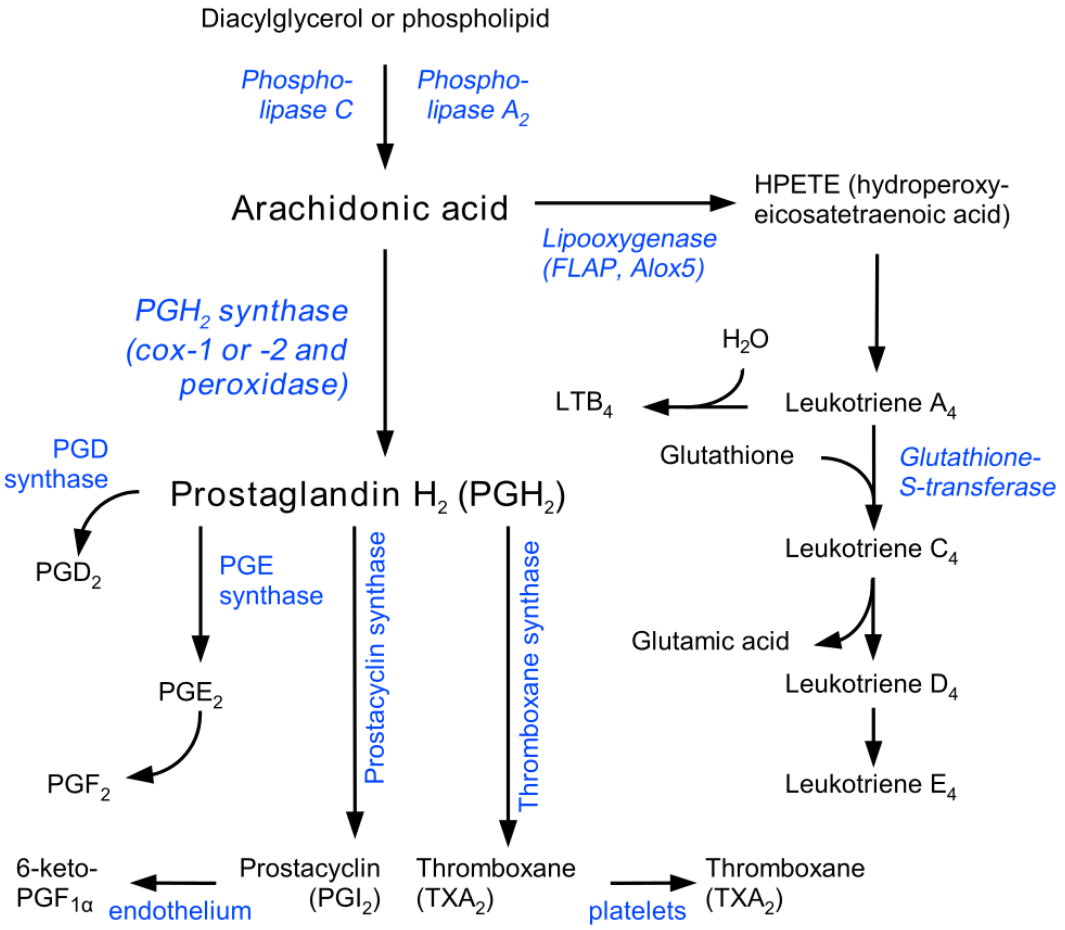


Figure-7: Biosynthesis of pain mediators.

Prostaglandins are found in most tissues and organs. They are produced by almost all nucleated cells. They are autocrine and paracrine lipid mediators that act upon platelets, endothelium, uterine and mast cells. They are synthesized in the cell from the fatty acid arachidonic acid. Arachidonic acid is created from diacylglycerol via phospholipase-A_2, then brought to either the cyclooxygenase pathway or the lipoxygenase pathway. The cyclooxygenase pathway produces thromboxane, prostacyclin and prostaglandin D, E and F. Alternatively, the lipoxygenase enzyme pathway is active in leukocytes and in macrophages and synthesizes leukotrienes.[10]

Release of prostaglandins from the cell

Prostaglandins were originally believed to leave the cells via passive diffusion because of their high lipophilicity. The discovery of the prostaglandin transporter (PGT, SLCO2A1), which mediates the cellular uptake of prostaglandin, demonstrated that diffusion alone cannot explain the penetration of prostaglandin through the cellular membrane. The release of prostaglandin has now also been shown to be mediated by a specific transporter, namely the multidrug resistance protein 4 (MRP4, ABCC4), a member of the ATP-binding cassette transporter superfamily. Whether MRP4 is the only transporter releasing prostaglandins from the cells is still unclear.

Cyclooxygenases

Prostaglandins are produced following the sequential oxygenation of arachidonic acid, DGLA or EPA by cyclooxygenases (COX-1 and COX-2) and terminal prostaglandin synthases. The classic dogma is as follows:

- COX-1 is responsible for the baseline levels of prostaglandins.
- COX-2 produces prostaglandins through stimulation.

However, while COX-1 and COX-2 are both located in the blood vessels, stomach and the kidneys, prostaglandin levels are increased by COX-2 in scenarios of inflammation and growth.

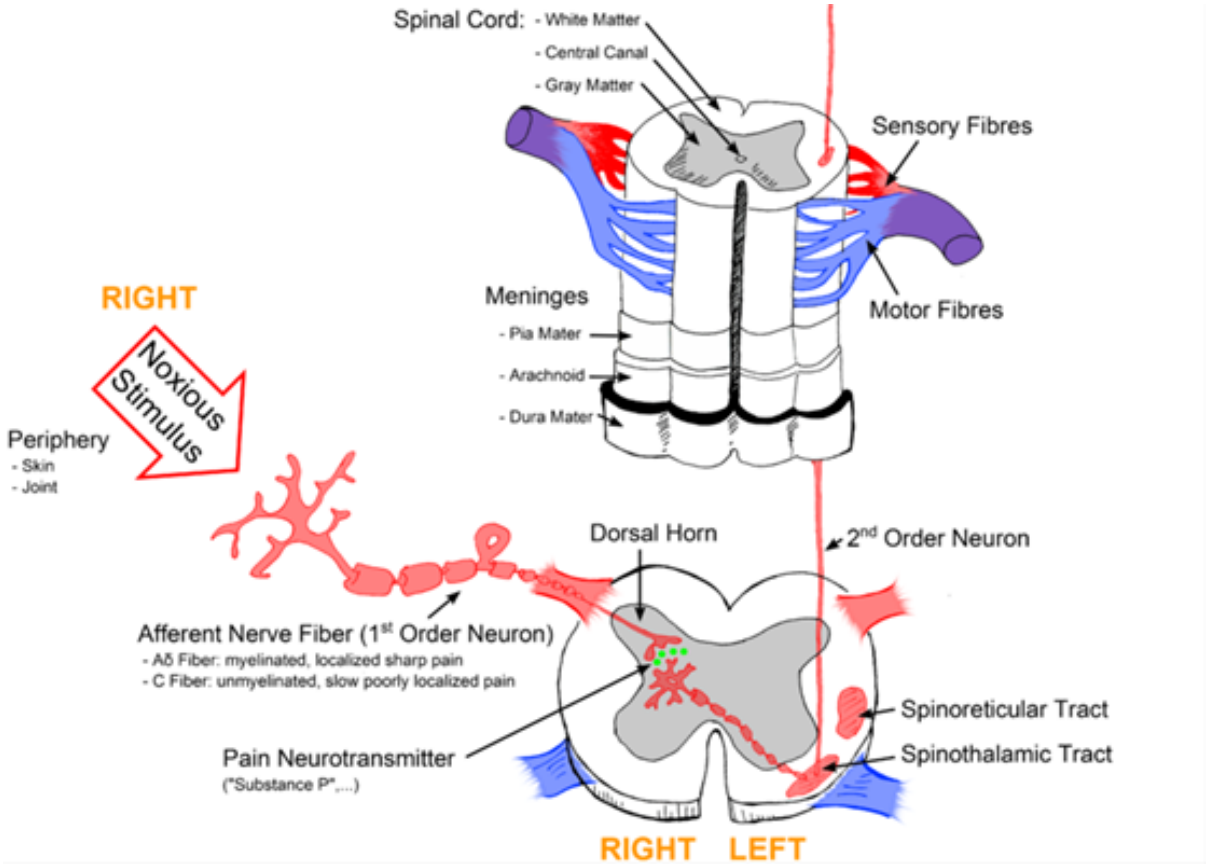


Figure-8: Spinal cord.

Prostaglandin E synthase

Prostaglandin E_2 (PGE_2) - the most abundant prostaglandin - is generated from the action of prostaglandin E synthases on prostaglandin H_2 (prostaglandin H_2, PGH_2). Several prostaglandin E synthases have been identified. To date, microsomal prostaglandin E synthase-1 emerges as a key enzyme in the formation of PGE_2.

Other terminal prostaglandin synthases

Terminal prostaglandin synthases have been identified that are responsible for the formation of other prostaglandins. For example, hematopoietic and lipocalin prostaglandin D synthases (hPGDS and lPGDS) are responsible for the formation of PGD_2 from PGH_2. Similarly, prostacyclin (PGI_2) synthase (PGIS) converts PGH_2 into PGI_2. A thromboxane synthase (TxAS) has also been identified. Prostaglandin-F synthase (PGFS) catalyzes the formation of 9α, 11β- PGF2α,β from PGD_2 and $PGF_{2\alpha}$ from PGH_2 in the presence of NADPH. This enzyme has recently been crystallized in complex with PGD_2 and bimatoprost (a synthetic analogue of $PGF_{2\alpha}$).

Functions

There are currently ten known prostaglandin receptors on various cell types. Prostaglandins ligate a sub-family of cell surface seven-transmembrane receptors, G-protein-coupled receptors. These receptors are termed DP1-2, EP1-4, FP, IP1-2, and TP, corresponding to the receptor that ligates the corresponding prostaglandin (e.g., DP1-2 receptors bind to PGD_2). The diversity of receptors means that prostaglandins act on an array of cells and have a wide variety of effects such as.

- create eicosanoids hormones
- acts on thermoregulatory center of hypothalamus to produce fever increases mating behaviors in goldfish.
- Prostaglandins are released during menstruation, due to the destruction of the endometrial cells, and the resultant release of their contents. Release of prostaglandins and other inflammatory mediators in the uterus cause the uterus to contract. These substances are thought to be a major factor in primary dysmenorrhea. Others say, that prostaglandins and leukotrienes are released during menstruation, due to the buildup of omega-6 fatty acids.[11]

Types

The following is a comparison of different types of prostaglandin, including prostaglandin I_2 (prostacyclin; PGI_2), prostaglandin D_2 (PGD_2), prostaglandin E_2 (PGE_2), and prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$).

Role in pharmacology

Inhibition

Examples of prostaglandin antagonists are

- NSAIDs (inhibit cyclooxygenase) and COX-2 selective inhibitors or coxibs
- Corticosteroids (inhibit phospholipase A_2 production)
- Cyclopentenone prostaglandins may play a role in inhibiting inflammation.

Type	Receptor	Receptor type	Function
PGI_2	IP	Gs	vasodilation, inhibit platelet aggregation, bronchodilation
PGD_2	PTGDR (DP_1) and $CRTH_2$ (DP_2)	GPCR	produced by mast cells; recruits Th_2 cells, eosinophils, and basophils In mammalian organs, large amounts of PGD_2 are found only in the brain and in mast cells. Critical to development of allergic diseases such as asthma
PGE_2	EP_1	Gq	bronchoconstriction, GI tract smooth muscle contraction
	EP_2	Gs	bronchodilation, GI tract smooth muscle relaxation vasodilation
	EP_3	Gi	↓ gastric acid secretion. ↑ gastric mucus secretion, uterus contraction (when pregnant), GI tract smooth muscle contraction. lipolysis inhibition, ↑ autonomic neurotransmitters, ↑ platelet response to their agonists and ↑ atherothrombosis *in-vivo*
	Unspecified		hyperalgesia, pyrogenic
$PGF_{2\alpha}$	FP	Gq	uterus contraction, bronchoconstriction

Table 1: Prostaglandins and pharmacology.

Clinical uses

Synthetic prostaglandins are used

- To induce childbirth (parturition) or abortion (PGE_2 or PGF_2, with or without mifepristone, a progesterone antagonist)
- To prevent closure of ductus arteriosus in newborns with particular cyanotic heart defects (PGE_1)
- As a vasodilator in severe Raynaud's phenomenon or ischemia of a limb
- In pulmonary hypertension
- In treatment of glaucoma (as in bimatoprost ophthalmic solution, a synthetic prostamide analog with ocular hypotensive activity) ($PGF_{2\alpha}$)
- To treat erectile dysfunction or in penile rehabilitation following surgery (PGE_1 as alprostadil).
- To measure erect penis size in a clinical environment
- To treat egg binding in small birds

Thromboxane

Thromboxane is a member of the family of lipids known as eicosanoids. The two major thromboxanes are thromboxane A_2 and thromboxane B_2.

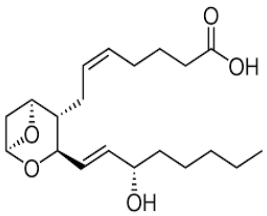
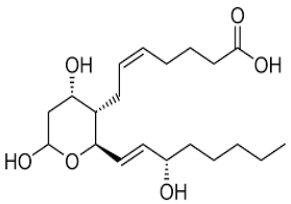


Figure-9: Thromboxane A_2



Thromboxane B_2

The distinguishing feature of thromboxanes is a 6-membered ether-containing ring. Thromboxane is named for its role in clot formation (thrombosis).

Production

Thromboxane-A synthase, an enzyme found in platelets, converts the arachidonic acid derivative prostaglandin H_2 thromoboxane.

Mechanism

Thromboxane acts by binding to any of the thromboxane receptors, G-protein- coupled receptors coupled to the G protein Gq.

Thromboxane is a vasoconstrictor and a potent hypertensive agent, and it facilitates platelet aggregation. It is in homeostatic balance in the circulatory system with prostacyclin, a related compound. The mechanism of secretion of thromboxanes from platelets is still unclear. They act in the formation of blood clots and reduce blood flow to the site of a clot. If the cap of a vulnerable plaque erodes or ruptures, as in myocardial infarction, platelets stick to the damaged lining of the vessel and to each other within seconds and form a plug. These "Sticky platelets" secrete several chemicals, including thromboxane A_2 that stimulate vasoconstriction, reducing blood flow at the site.

Role of A_2 in platelet aggregation

Thromboxane A_2 (TXA_2), produced by activated platelets, has prothrombotic properties, stimulating activation of new platelets as well as increasing platelet aggregation. Platelet aggregation is achieved by mediating expression of the glycoprotein complex GP IIb/IIIa in the cell membrane of platelets. Circulating fibrinogen binds these receptors on adjacent platelets, further strengthening the clot.

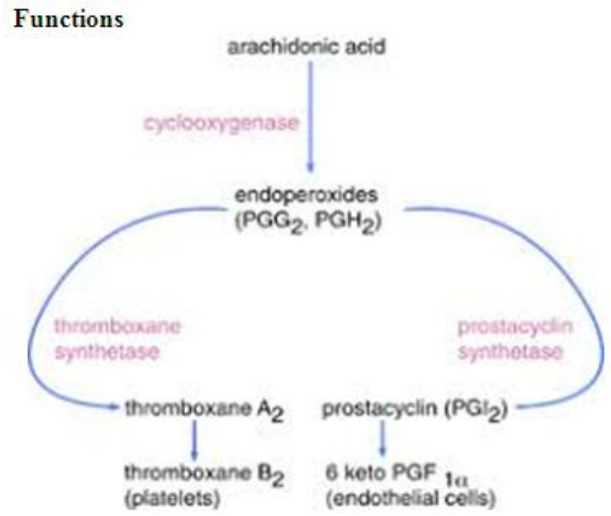


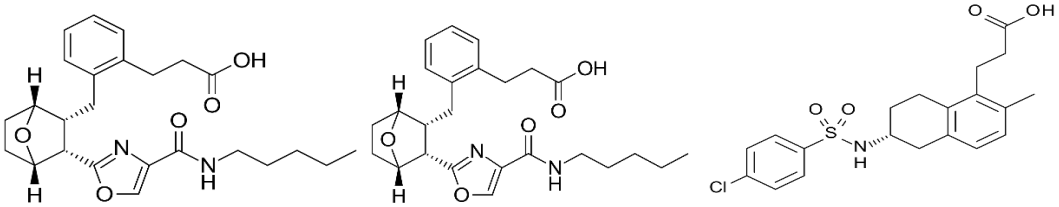
Figure-10: Thromboxane biosynthesis.

Pathology

It is believed that the vasoconstriction caused by thromboxanes plays a role in Prinzmetal's angina. Omega-3 fatty acids are metabolized to produce higher levels of TxA, which is relatively less potent than TxA_2 and PGI_3; therefore, there is a balance shift toward inhibition of vasoconstriction and platelet aggregation. It is believed that this shift in balance lowers the incidence of myocardial infarction (heart attack) and stroke. Vasoconstriction and, perhaps, various proinflammatory effects exerted by TxA on tissue microvasculature, is probable reason why the TxA is pathogenic in various diseases, such as ischemia-reperfusion injury., hepatic inflammatory processes, acute hepatotoxicity etc. TxB_2, a stable degradation product of TxA_2, plays a role in acute hepatoxicity induced by acetaminophen.

Inhibitors: Thromboxane inhibitors are broadly classified as either those that inhibit the synthesis of thromboxane, or those that inhibit the target effect of it. Thromboxane synthesis inhibitors, in turn, can be classified regarding which step in the synthesis they inhibit.

- The widely used drug aspirin acts by inhibiting the ability of the COX enzyme to synthesize the precursors of thromboxane within platelets. Low-dose, long-term aspirin use irreversibly blocks the formation of thromboxane A_2 in platelets, producing an inhibitory effect on platelet aggregation. This anticoagulant property makes aspirin useful for reducing the incidence of heart attacks. 40 mg of aspirin a day is able to inhibit a large proportion of maximum thromboxane A_2 release provoked acutely, with the prostaglandin I_2 synthesis being little affected; however, higher doses of aspirin are required to attain further inhibition.
- Thromboxane synthase inhibitors inhibit the final enzyme (thromboxane synthase) in the synthesis of thromboxane. Ifetroban is a potent and selective thromboxane receptor antagonist. Dipyridamole antagonizes this receptor too, but has various other mechanisms of antiplatelet activity as well.
- High-dose naproxen can induce near-complete suppression of platelet thromboxane throughout the dosing interval and appears not to increase cardiovascular disease (CVD) risk, whereas other high-dose NSAID (non- steroidal-anti-inflammatory) regimens have only transient effects on platelet COX-1 and have been found to be associated "with a small but definite vascular hazard". The inhibitors of the target effects of thromboxane are the thromboxane receptor antagonist, including terutroban.[12]



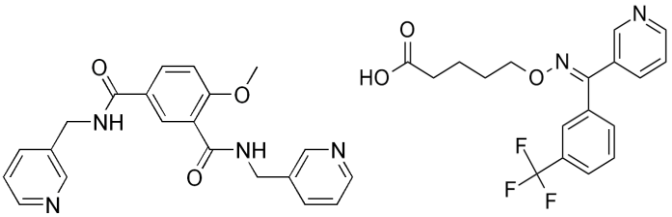


Figure-11: Drugs.

Picotamide has activity both as a thromboxane synthase inhibitor and as a thromboxane receptor antagonist. Ridogrel is another example.

Leukotriene

LTA_4 Note the four double bonds, three of them conjugated. This is a common property of A_4, B_4, C_4, D_4, and E_4. LTC_4 is a cysteinyl leukotriene, as are D_4 and E_4.

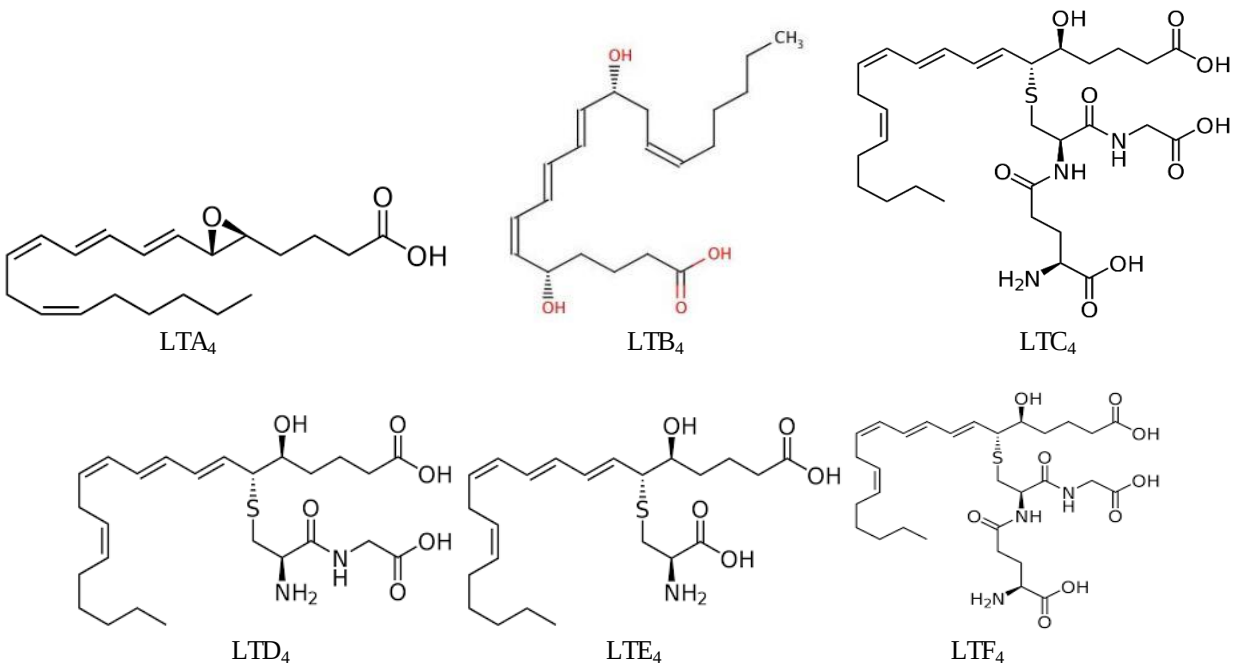


Figure-12: Leukotrienes.

Leukotrienes are a family of eicosanoid inflammatory mediators produced in leukocytes by the oxidation of arachidonic acid (AA) and the essential fatty acid eicosapentaenoic acid (EPA) by the enzyme arachidonate 5-lipoxygenase. Leukotrienes use lipid signaling to convey information to either the cell producing them (autocrine signaling) or neighboring cells (paracrine signaling) in order to regulate immune responses. The production of leukotrienes is usually accompanied by the production of histamine and prostaglandins, which also act as inflammatory mediators. One of their roles (specifically, leukotriene D_4) is to trigger contractions in the smooth muscles lining the bronchioles; their overproduction is a major cause of inflammation in asthma and allergic rhinitis. Leukotriene antagonists are used to treat these disorders by inhibiting the production or activity of leukotrienes.

History and name

The name *leukotriene*, introduced by Swedish biochemist Bengt Samuelsson in 1979, comes from the words *leukocyte* and *triene* (indicating the compound's three conjugated double bonds). What would be later named leukotriene C, "slow reaction smooth muscle-stimulating substance" (SRS) was originally described between 1938 and 1940 by Feldberg and Kellaway. The researchers isolated SRS from lung tissue after a prolonged period following exposure to snake venom and histamine. Leukotrienes are commercially available to the research community.[13]

Figure-13: Bengt Samuelsson.

Types

Cysteinyl leukotrienes

LTC_4, LTD_4, LTE_4 and LTF_4 are often called **cysteinyl leukotrienes** due to the presence of the amino acid cysteine in their structure. The cysteinyl leukotrienes make up the slow-reacting substance of anaphylaxis (SRS-A). LTF_4, like LTD_4, is a metabolite of LTC_4, but, unlike LTD_4, which lacks the glutamic residue of glutathione, LTF_4 lacks the glycine residue of glutathione.

LTB_4

Leukotriene B_4

LTB_4 is synthesized *in-vivo* from LTA_4 by the enzyme LTA_4 hydrolase. Its primary function is to recruit neutrophils to areas of tissue damage, though it also helps promote the production of inflammatory cytokines by various immune cells. Drugs that block the actions of LTB_4 have shown some efficacy in slowing the progression of neutrophil-mediated diseases.

LTG_4

There has also been postulated the existence of LTG_4, a metabolite of LTE_4 in which the cysteinyl moiety has been oxidized to an alpha-keto-acid (i.e.—the cysteine has been replaced by a pyruvate). Very little is known about this putative leukotriene.]

LTB_5

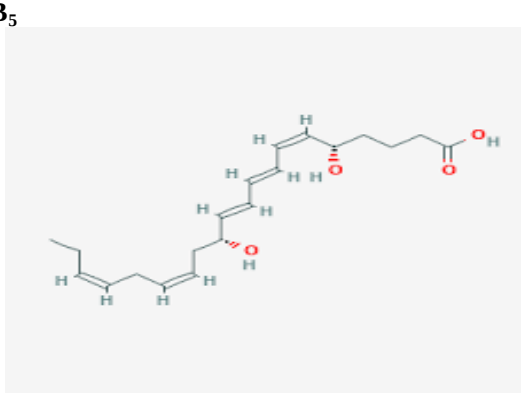


Figure-14: LTB_5

Leukotrienes originating from the omega-3 class eicosapentanoic acid (EPA) have diminished inflammatory effects. LTB_5 induces aggregation of rat neutrophils, chemokinesis of human polymorphonuclear neutrophils (PMN), lysosomal enzyme release from human PMN and potentiation of bradykinin-induced plasma exudation, although compared to LTB_4, it has at least 30 times less potency.

Biochemistry

Synthesis

Leukotrienes are synthesized in the cell from arachidonic acid by arachidonate 5- lipoxygenase. The catalytic mechanism involves the insertion of an oxygen moiety at a specific position in the arachidonic acid backbone. The lipoxygenase pathway is active in leukocytes and other immunocompetent cells, including mast cells, eosinophils, neutrophils, monocytes, and basophils. When such cells are activated, arachidonic acid is liberated from cell membrane phospholipids by phospholipase A_2, and donated by the 5-lipoxygenase-activating protein (FLAP) to 5-lipoxygenase. 5-Lipoxygenase (5-LO) uses FLAP to convert arachidonic acid into 5- hydroperoxyeicosatetraenoic acid (5-HPETE), which spontaneously reduces to 5-hydroxyeicosatetraenoic acid (5-HETE). The enzyme 5-LO acts again on 5-HETE to convert it into leukotriene A_4 (LTA_4), an unstable epoxide. 5-HETE can be further metabolized to 5-oxo-ETE and 5-oxo-15-hydroxy-ETE, all of which have pro- inflammatory actions similar but not identical to those of LTB_4 and mediated not by LTB_4 receptors but rather by the OXE receptor. In cells equipped with LTA hydrolase, such as neutrophils and monocytes, LTA_4 is converted to the dihydroxy acid leukotriene LTB_4, which is a powerful chemoattractant for neutrophils acting at BLT_1 and BLT_2 receptors on the plasma membrane of these cells. In cells that express LTC_4 synthase, such as mast cells and eosinophils, LTA_4 is conjugated with the tripeptide glutathione to form the first of the cysteinyl- leukotrienes, LTC_4. Outside the cell, LTC_4 can be converted by ubiquitous enzymes to form successively LTD_4 and LTE_4, which retain biological activity.

The cysteinyl-leukotrienes act at their cell-surface receptors $CysLT_1$ and $CysLT_2$ on target cells to contract bronchial and vascular smooth muscle, to increase permeability of small blood vessels, to enhance secretion of mucus in the airway and gut, and to recruit leukocytes to sites of inflammation. Both LTB_4 and the cysteinyl-leukotrienes (LTC_4, LTD_4, LTE_4) are partly degraded in local tissues, and ultimately become inactive metabolites in the liver.

Function

Leukotrienes act principally on a subfamily of G protein-coupled receptors. They may also act upon peroxisome proliferator-activated receptors. Leukotrienes are involved in asthmatic and allergic reactions and act to sustain inflammatory reactions.

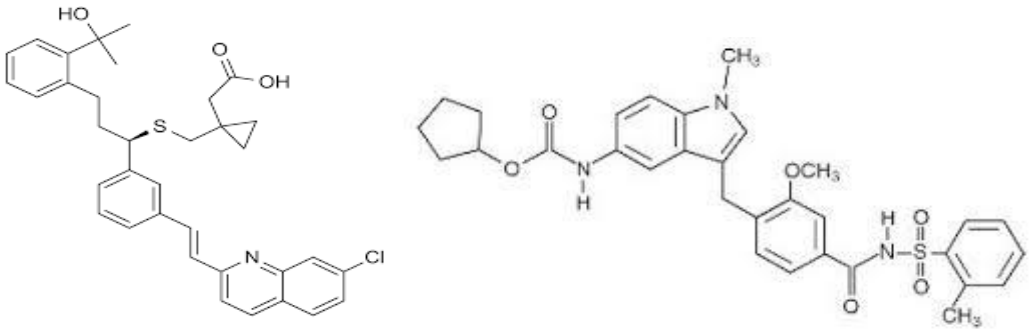


Figure-15: Montelukast and Zafirlukast.

Several leukotriene receptor antagonists such as montelukast and zafirlukast are used to treat asthma. Recent research points to a role of 5-lipoxygenase in cardiovascular and neuropsychiatric illnesses. Leukotrienes are very important agents in the inflammatory response. Some such as LTB4 have a chemotactic effect on migrating neutrophils, and as such help to bring the necessary cells to the tissue. Leukotrienes also have a powerful effect in bronchoconstriction and increase vascular permeability.[14]

Leukotrienes in asthma

Leukotrienes contribute to the pathophysiology of asthma, especially in patients with aspirin-exacerbated respiratory disease (AERD), and cause or potentiate the

following symptoms.

- airflow obstruction
- increased secretion of mucus
- mucosal accumulation
- bronchoconstriction
- infiltration of inflammatory cells in the airway wall

Role of cysteinyl leukotrienes

Cysteinyl leukotriene receptors $CYSLTR_1$ and $CYSLTR_2$ are present on mast cells, eosinophil, and endothelial cells. During cysteinyl leukotriene interaction, they can stimulate proinflammatory activities such as endothelial cell adherence and chemokine production by mast cells. As well as mediating inflammation, they induce asthma and other inflammatory disorders, thereby reducing the airflow to the alveoli. The levels of cysteinyl leukotrienes, along with 8-isoprostane, have been reported to be increased in the EBC of patients with asthma, correlating with disease severity. Cysteinyl leukotrienes may also play a role in adverse drug reactions in general and in contrast medium induced adverse reactions in particular. In excess, the cysteinyl leukotrienes can induce anaphylactic shock.

Leukotrienes in dementia

Leukotrienes are found to play an important role in the later stages of Alzheimer's disease and related dementias in studies with animals. In tau transgenic mice, which develop tau pathology, "zileuton, a drug that inhibits leukotriene formation by blocking the 5-lipoxygenase enzyme" was found to reverse memory loss.

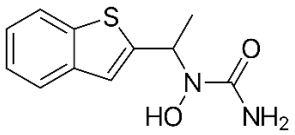


Figure-16: Zileuton.

Pain Pathway

Medication

Acute pain is usually managed with medications such as analgesics and anesthetics. Caffeine when added to pain medications such as ibuprofen, may provide some additional benefit. Ketamine can be used instead of opioids for short term pain. Management of chronic pain, however, is more difficult, and may require the coordinated efforts of a pain management team, which typically includes medical practitioners, clinical pharmacists, clinical psychologists, physiotherapists, occupational therapists, physician assistants, and nurse practitioners. Sugar (sucrose) when taken by mouth reduces pain in newborn babies undergoing some medical procedures (a lancing of the heel, venipuncture, and intramuscular injections). Sugar does not remove pain from circumcision, and it is unknown if sugar reduces pain for other procedures. Sugar did not affect pain-related electrical activity in the brains of newborns one second after the heel lance procedure. Sweet liquid by mouth moderately reduces the rate and duration of crying caused by immunization injection in children between one and twelve months of age.

Psychological

Individuals with more social support experience less cancer pain, take less pain medication, report less labor pain and are less likely to use epidural anesthesia during childbirth, or suffer from chest pain after coronary artery bypass surgery. Suggestion can significantly affect pain intensity. About 35% of people report marked relief after receiving a saline injection they believed to be morphine. This placebo effect is more pronounced in people who are prone to anxiety, and so anxiety reduction may account for some of the effect, but it does not account for all of it. Placebos are more effective for intense pain than mild pain; and they produce progressively weaker effects with repeated administration. It is possible for many with chronic pain to become so absorbed in an activity or entertainment that the pain is no longer felt, or is greatly diminished.

Cognitive behavioral therapy (CBT) has been shown effective for improving quality of life in those with chronic pain but the reduction in suffering is modest, and the CBT method was not shown to have any effect on outcome. Acceptance and Commitment Therapy (ACT) may also be effective in the treatment of chronic pain.

A number of meta-analyses have found clinical hypnosis to be effective in controlling pain associated with diagnostic and surgical procedures in both adults and children, as well as pain associated with cancer and childbirth. A 2007 review of 13 studies found evidence for the efficacy of hypnosis in the reduction of chronic pain under some conditions, though the number of patients enrolled in the studies was low, raising issues related to the statistical power to detect group differences, and most lacked credible controls for placebo or expectation.

Alternative medicine

Pain is the most common reason for people to use complementary and alternative medicine. An analysis of the 13 highest quality studies of pain treatment with acupuncture, published in January 2009, concluded there was little difference in the effect of real, faked and no acupuncture. However, other reviews have found some benefit. Additionally, there is tentative evidence for a few herbal medicines. There has been some interest in the relationship between vitamin D and pain, but the evidence so far from controlled trials for such a relationship, other than in osteomalacia, is inconclusive. For chronic (long-term) lower back pain, spinal manipulation produces tiny, clinically insignificant, short-term improvements in pain and function, compared sham therapy and other interventions. Spinal manipulation produces the same outcome as other treatments, such as general practitioner care, pain-relief drugs, physical therapy, and exercise, for acute (short-term) lower back pain.[15]

Epidemiology

Pain is the main reason for visiting an emergency department in more than 50% of cases, and is present in 30% of family practice visits. Several epidemiological studies have reported widely varying prevalence rates for chronic pain, ranging from 12 to 80% of the population. It becomes more common as people approach death. A study of 4,703 patients found that 26% had pain in the last two years of life, increasing to 46% in the last month. A survey of 6,636 children (0–18 years of age) found that, of the 5,424 respondents, 54% had experienced pain in the preceding three months. A quarter reported having experienced recurrent or continuous pain for three months or more, and a third of these reported frequent and intense pain. The intensity of chronic pain was higher for girls, and girls' reports of chronic pain increased markedly between ages 12 and 14.

CONCLUSION

Each mammal in the world face the feelings of pain either human or animal. Pain is mediated my any traumatic condition either by physiological malfunction or by any kind of accidental hits on the body surface. The origin of pain is due to phospholipase A_2 a phosphorylated enzyme mediated lipid which generates the pain pathway by following three biogenic mediators: prostaglandins, thromboxanes and leukotrienes. All three are C-20 carbon compounds having free -COOH groups that potentiates the arachidonic acid pathway and the drugs which inhibit this pathway have also free -COOH so inhibition of pain pathway is possible by competitive inhibition of cyclooxygenase pathway to stop the biosynthesis of pain mediators.

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